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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,371	04/30/2002	Maria Cristina Geroni	217550US0PCT	2516

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EXAMINER

KRISHNAN, GANAPATHY

ART UNIT.	PAPER NUMBER
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1623

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 10/031,371	<b>Applicant(s)</b> GERONI ET AL.	
	<b>Examiner</b> Ganapathy Krishnan	<b>Art Unit</b> 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 0 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 17, 18, 20-25, 27-32, 36-38 and 40-44 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 17, 18, 20-25, 27-31, 32, 36-38 and 40-44 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date ____. | 6) <input type="checkbox"/> Other: ____.  |

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### **DETAILED ACTION**

The amendment filed March 2, 2004 has been received, entered and carefully considered.

The following information provided in the amendment affects the instant application:

1. Claims 1-16, 19, 26, 31, 33, 35 and 39 have been canceled.
2. New Claims 40-44 have been added.
3. Claims 17, 18, 20-25, 27, 30, 32 and 38 have been amended.
4. Remarks drawn to rejections under 35 USC 112, second paragraph.

Claims 17, 18, 20-25, 27-30, 32, 36-38 and 40-44 are pending in the case.

The text of those sections of Title 35, U. S. Code not included in this action can be found in a prior Office action.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17, 18, 20-25, 27-30, 32, 36-38 and 40-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a synergistic composition comprising gemcitabine and the anthracycline Ia (compound Ia), does not reasonably provide enablement for a synergistic composition comprising compound Ib and Ia and any other antimetabolite compound including 5-fluorouracil. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

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A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

- (A) The breadth of the claims
- (B) The state of the prior art
- (C) The level of one of ordinary skill
- (D) The level of predictability in the art
- (E) The amount of direction provided by the inventor
- (F) The existence of working examples
- (G) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

#### **The breadth of the claims**

Claims 17, 18, 20-25 and 27 are drawn to a synergistic antineoplastic composition comprising the anthracycline Ia or Ib and an antimetabolite compound that includes 5-fluorouracil and gemcitabine that are analogs of pyrimidine and cytidine and claims 28-30, 32, 36-38 and 40-44 are drawn to methods of treating metastasis in mammals comprising administering the said composition. The breadth of the claims is seen to include a composition comprising the said alkylating agents with any of the several antimetabolite compounds known other than gemcitabine and 5-fluorouracil.

#### **The state of the prior art**

The examiner notes that the art cited by the applicants (Cancer, Principles and Practice of Oncology, 1997, 432-452). However these compounds have structural differences including differences in substitution patterns and are not correlative for the

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claimed synergistic composition and the synergistic effect in the method of treatment of the said disease.

**The level of predictability in the art**

The examiner acknowledges the probability and predictability that the instantly claimed synergy of the composition and method of treatment of metastasis would have a reasonable expectation of success. There is not seen sufficient data to substantiate the synergism between anthracycline Ia and any antimetabolite, anthracycline Ib and any metabolite other than the combination of compound Ia and gemcitabine and the synergistic effect of the composition in the said method of treatment. Synergism between two active agents is highly unpredictable.

**The amount of direction provided by the inventor**

The instant specification is not seen to provide enough guidance that would allow a skilled artisan to extrapolate from the disclosure and the examples provided to predict the synergism between compounds Ia or Ib and any metabolite other than gemcitabine and also predict the synergistic effect of the combination when used in a method of treatment of the said disease. The specification also fails to direct the skilled artisan in correlative prior art procedures which might provide the basis for such a prediction.

**The existence of working examples**

The working examples set forth in the instant specification are drawn to the combination of the anthracycline Ia (PNU-159548) and gemcitabine in particular. Despite this example there is little enabling disclosure for the combination of the anthracycline Ia and any antimetabolite other than gemcitabine. Applicants have given a

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working example of anthracycline Ia and gemcitabine only and are therefore not entitled to the combinations of other antimetabolites with compound Ia and Ib too.

**The quantity of experimentation needed to make or use the invention based on the content of the disclosure**

Indeed, in view of the information set forth, the instant disclosure is not seen to be enabling for a synergistic composition comprising compound Ia or Ib with any antimetabolite. The only enabling disclosure is the composition comprising compound Ia and gemcitabine. One of ordinary skill in the art would have to perform undue experimentation in order to determine the combinations of compound Ia or Ib and an antimetabolite to determine if there is synergism.

***Conclusion***

Claims 17, 18, 20-25, 27-30, 32, 36-38 and 40-44 are rejected.

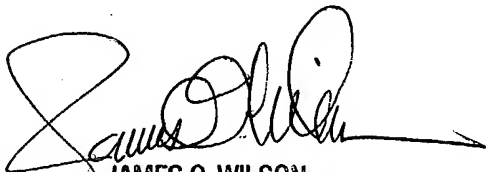
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

GK



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